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Using laboratory measurements to predict in-flight desaturation in respiratory patients: Are current guidelines appropriate?

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Summary
In an attempt to guide physicians asked by respiratory patients for advice on flight fitness, the British Thoracic Society (BTS) have published guidelines on fitness to fly. The main potential hazard is hypobaric hypoxia, and efforts have focused on the prediction of hypoxia in individuals. The present study examines 10 years' experience of hypoxic challenge (HC) of respiratory patients to evaluate if the guidelines recommended by the BTS are appropriate.

One hundred and eighteen patients (67 female, mean age 65.6 $\pm$ 11.4 (SD) years) were referred for assessment. Patients underwent HC using a 40% Venturi mask supplied with 100% N_2 which lowered the F_iO_2 to 15.1%. A further 13 patients on long-term oxygen therapy also underwent HC whilst receiving supplemental oxygen.

In agreement with the BTS guidelines, all patients with a sea level SpO_2 of over 95% maintained their $SpO_2 \geq 90\%$ during HC. One third of patients with sea level SpO_2 of 92–95%, but no other risk factor (as defined by the guidelines) also desaturated below 90% during HC. Thirty-two patients were assessed as fit to fly with supplemental oxygen.

Our results support the BTS guidelines for patients with a sea level SpO_2 >95% but suggest that some revision is required for patients with a sea level SpO_2 of 92–95%. It was not possible to predict from either initial SpO_2 or spirometry which individuals were at risk of desaturation below 90% during hypoxic challenge.

Introduction

Air travel is rapidly increasing worldwide, therefore more patients with respiratory disease will be wanting to fly. As a consequence of this, patients with respiratory disease are likely to ask their doctors "am I fit to fly?" At normal

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cruising altitudes commercial aircraft are designed to maintain a reduced cabin pressure which is equivalent to an altitude of not greater than 2438 m. At this altitude the pO_2 is reduced to a value equivalent to an inspired fraction of oxygen (FiO_2) of 15.1% at sea level. The sigmoid shape of the oxygen dissociation curve allows healthy individuals to tolerate this reduction in pO_2 without significant hypoxaemia, but passengers with respiratory disease may not be able to increase their ventilation sufficiently to compensate for the reduced pO_2, leading to alveolar and tissue hypoxia.

To predict which patients with lung disease may be hypoxic during flight a number of assessment protocols have been developed.[1–3] The British Thoracic Society (BTS) and Aerospace Medical Association (AMA) have published comprehensive guidelines[4,5] to assist clinicians in advising their patients. Both sets of guidelines recommend hypoxic challenge as a means of identifying passengers at risk of significant hypoxia during flight. The BTS Guidelines suggest that hypoxic challenge is unnecessary for any patient with an O_2 saturation (SpO_2) $>95\%$ and that those with an SpO_2 $<92\%$ should fly with supplemental oxygen. For patients with an SpO_2 between 92% and 95% with additional risk factors, such as hypercapnia, restrictive disease or an FEV_1 $<50\%$ predicted, the guidelines suggest a hypoxic challenge. Our laboratory has been performing hypoxic challenge to assess flight fitness since 1997, and the data collected over the last ten years have been evaluated to examine if the BTS criteria are valid.

Methods

Patients

One hundred and eighteen patients (67 female, mean age 65.6 ± 11.4 (SD) years) were referred to the laboratory (altitude 30 m above sea level) for assessment of flight fitness. Referrals came from hospital and primary care physicians, primarily at the request of the patient. As this assessment is one of the routine clinical assessments made by our laboratory and we are reporting an audit of the outcome of these assessments, we were advised that formal Ethics Committee approval was not required. The patients were classified into disease groups using only the information included in the referral form or letter. Most patients (63%) had a diagnosis of chronic obstructive pulmonary disease (COPD) (see Table 1 for a full breakdown of diagnosis). Seventy-eight patients were ex-smokers, 18 were current smokers and the remaining 22 non-smokers. Spirometric data (FEV_1 and VC) were compared with appropriate reference values.[6] Only patients who were clinically stable, i.e. no self-reported deterioration in their condition or who had not been prescribed antibiotics or had any change in oral steroid therapy within the previous 4 weeks, were considered for assessment.

Hypoxic challenge protocol and interpretation

Oxygen saturation was recorded continuously throughout the assessment and the values noted at 30-s intervals during a 5-min period of rest, breathing room air, using an earlobe probe connected to a pulse oximeter (Model 3740; Ohmeda, Guilford, UK). Before measurements of SpO_2 were made the patient's earlobe was prepared by rubbing with a topical vasodilator cream (Ralgex®, Seton Medical Group, Oldham, UK).

All patients with a sea level SpO_2 $\geq 90\%$ underwent a 20-min hypoxic challenge (HC). The decision to perform hypoxic challenge in all these subjects, not just those with a starting SpO_2 of 95% or under predates the BTS guidelines and provides the opportunity for a clinical validation of the BTS 95% cut-off value. The method of Vohra and Klocke[7] was used, which employs a 40% Venturi mask, supplied with 10 L/min 100% N_2 to lower the patient's F_iO_2 to 0.15. The accuracy of the F_iO_2 was checked using an oxygen sensor sampling directly from just outside the mouth. Inspired oxygen was 0.15 in 15 healthy subjects and 6 COPD patients with an intersubject standard deviation of 0.02.

The results of hypoxic challenge were interpreted according to a locally derived algorithm (which predates the BTS guidelines) described elsewhere[8] and shown in Fig. 1. If SpO_2 remained $\geq 90\%$ during HC, patients were classed as fit to fly without supplemental O_2 (Group A). If SpO_2 fell below 90% during HC, patients were given supplemental oxygen (2 L/min via nasal cannulae placed under the Venturi mask) and the HC repeated once SpO_2 had stabilised. If SpO_2 remained $\geq 90\%$, patients were classified as fit to fly with supplemental O_2 (Group B). If the SpO_2 still fell below 90%, the HC would be stopped, the flow of supplemental O_2 increased to 4 L/min and a third HC performed. If the SpO_2 still remained $<90\%$ patients were classified as likely to be hypoxic even with supplemental oxygen, and they were advised against air travel (Group C).

An additional 13 patients were referred who were receiving long-term oxygen therapy (LTOT). In these, hypoxic challenge began with them receiving 2 L/min supplemental O_2 (by nasal cannulae placed under the Venturi mask) throughout the assessment. If their SpO_2 remained $\geq 90\%$ during HC they were classified in Group B. If SpO_2 fell below 90% on HC the flow of O_2 was increased to 4 L/min and HC was repeated. If SpO_2 remained $\geq 90\%$ they were classified as fit to fly with increased supplemental O_2 (group B). If SpO_2 still fell to $<90\%$ they were advised against air travel (Group C).

Statistical analyses were carried out using a commercial statistical package (Sigmastat, SPSS, UK). To examine which variables might predict desaturation, scatter plots of FEV_1 (both absolute values and % predicted) against percentage desaturation on HC were inspected. All data were subjected to the Kolmogorov–Smirnov normality test. As data were not normally distributed, Spearman rank correlations were used. A probability value of <0.05 was considered statistically significant.

Results

Hypoxic challenge

Ninety patients (76% of the study group) were able to maintain SpO_2 $\geq 90\%$ during HC (Group A). Twenty-seven patients (23% of the study group) required supplemental oxygen (2 L/min) to maintain SpO_2 $\geq 90\%$ during HC (Group B).

Table 1 Patient details, broken down by the primary diagnosis recorded on the request form

Primary diagnosis	No. of patients assessed	Age	FEV_1	VC	FEV_1/VC ratio	% predicted FEV_1	% predicted VC
		Years	Litres	Litres			
COPD	74	68.6 ± 8.5	1.14 ± 0.55	2.50 ± 0.85	46.6 ± 15.8	47 ± 21	77 ± 17
Interstitial lung disease	18	67.3 ± 9.5	1.48 ± 0.76	2.11 ± 0.82	69.0 ± 19.1	60 ± 27	68 ± 21
CF or bronchiectasis	8	55.0 ± 18.3	1.86 ± 0.68	2.56 ± 0.83	74.0 ± 15.1	67 ± 28	70 ± 23
Asthma	5	52.2 ± 16.6	1.44 ± 0.63	2.37 ± 0.32	59.4 ± 24.0	58 ± 30	79 ± 20
Obstructive sleep apnoea	3	57.0 ± 12.0	1.67 ± 0.37	2.70 ± 0.96	65.0 ± 20.0	63 ± 21	75 ± 19
Previous pneumonia	3	62.5 ± 9.0	1.83 ± 1.44	2.97 ± 1.80	58.7 ± 16.6	63 ± 20	83 ± 16
Neuromuscular disease	2	51.2 ± 2.0	0.88 ± 0.18	1.05 ± 0.35	85.3 ± 11.9	45 ± 15	44 ± 23
Pulmonary vascular disease	2	60.3 ± 15.9	2.14 ± 0.66	3.03 ± 1.24	72.2 ± 7.8	68 ± 9	78 ± 12
Thoracic neoplasm	2	70.7 ± 4.4	1.40 ± 0.14	2.55 ± 1.06	61.4 ± 31.1	43 ± 3	61 ± 26
Previous ARDS	1	36	1.90	2.10	90	45	40

Mean $\pm$ 1 SD values for absolute values and % predicted FEV_1 and VC are shown.

Only one patient was considered too hypoxic to risk travelling (Group C).

Of the additional 13 patients on LTOT, 8 maintained SpO_2 $\geq$90% on HC while receiving supplemental O_2 at 2 L/min and 4 patients required increased supplemental O_2 (4 L/min) to maintain SpO_2 $\geq$90%. One patient was unable to maintain their SpO_2 >90% even with the addition of 4 L/min supplemental O_2.

With reference to the BTS guidelines, results confirm that all patients with a sea level SpO_2 >95% did not desaturate to <90% on hypoxic challenge (Fig. 2). The BTS guidelines suggest that patients with a sea level SpO_2 between 92% and 95% only require hypoxic challenge if they also have additional risk factors. In the present study 59 patients not on LTOT had a sea level SpO_2 between 92% and 95%. Thirty-eight (64%) of these had additional risk factors as defined by the BTS (31 with FEV_1 <50% predicted value and 7 with restrictive and/or interstitial disease).

Thirty-four patients (of the 59 with a sea level SpO_2 between 92% and 95%) were fit to fly without oxygen (Group A) and 25 required supplemental O_2 (Group B). Seven patients categorised as requiring supplemental oxygen during flight had no additional BTS-defined risk factors.

Relationship between sea level SpO_2, spirometry and response to hypoxic challenge

Fig. 3 shows the absolute desaturation observed during hypoxic challenge plotted against level of sea level oxygen saturation for all patients not on LTOT. As expected from the oxygen dissociation curve, Figure 3 shows a weak, but statistically significant trend towards greater desaturation on

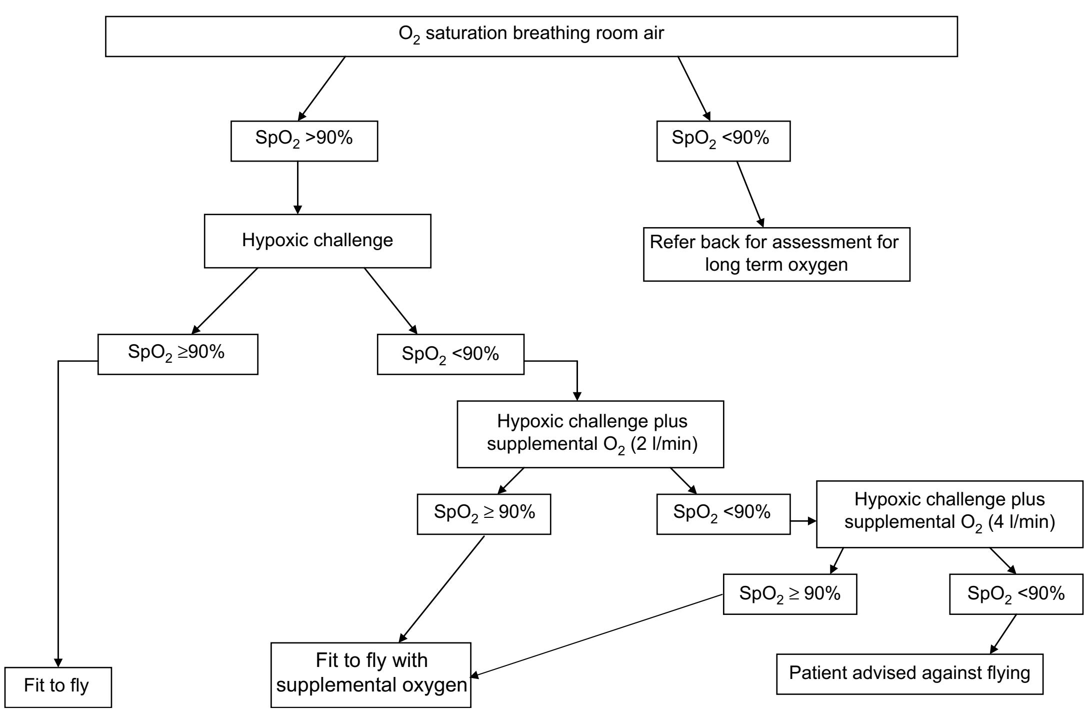

Figure 1 Hypoxic challenge interpretation algorithm.

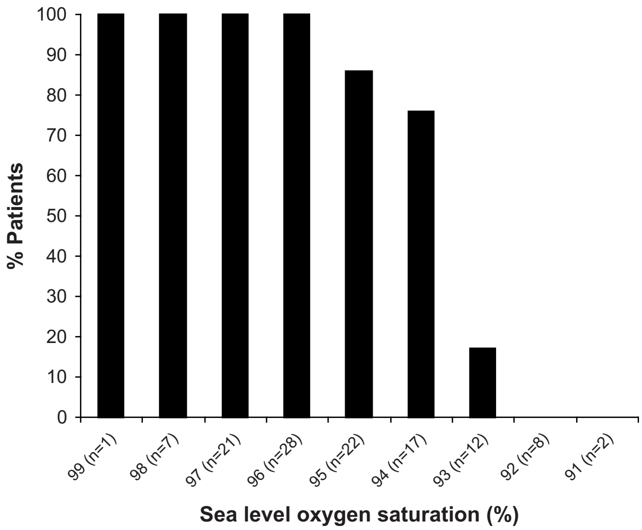

Figure 2 Percentage of all patients not on LTOT undergoing hypoxic challenge who were able to maintain their O_2 saturation above 90%, subdivided by pre-test sea level O_2 saturation.

hypoxic challenge in patients with lower sea level saturation, but with marked variability ($R = -0.312$, $P < 0.001$). There was no correlation between disease severity as measured by FEV_1 (% predicted) and either initial SpO_2 or the lowest SpO_2 recorded during hypoxic challenge, either in the patient group as a whole ($R = 0.116$ and 0.123 respectively) or in the subset with COPD ($R = 0.127$ and 0.070 respectively). Similarly, there was no correlation between % predicted FEV_1 and the degree of desaturation on HC ($R = -0.149$, $P = 0.108$) (Fig. 4).

Influence of diagnostic category on response to hypoxic challenge

Table 2 shows the results for each diagnostic category. In this data set, there was no significant effect (z-test) of diagnostic category on the response to hypoxic challenge.

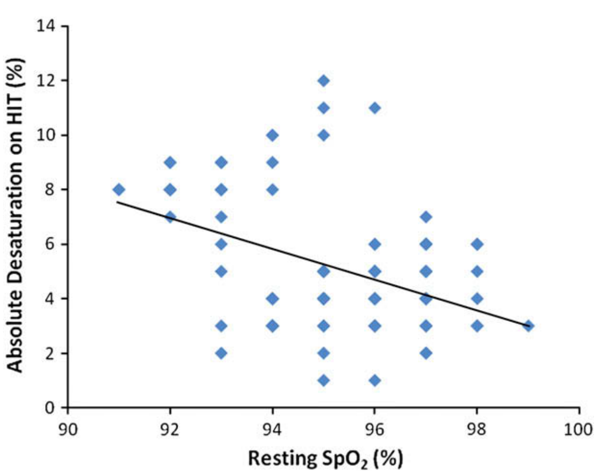

Figure 3 Correlation between pre-test sea level O_2 saturation and absolute desaturation on hypoxic challenge for all patients not on LTOT.

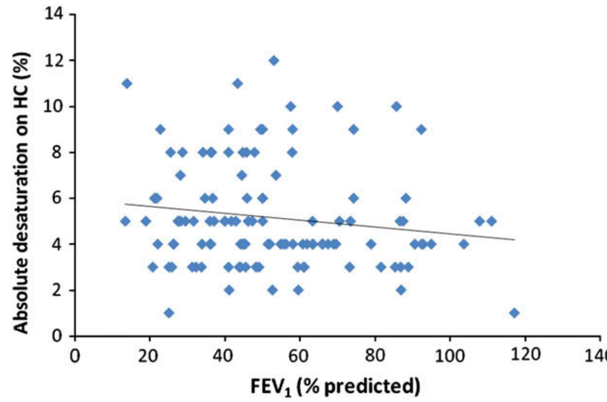

Figure 4 Relationship between FEV_1 (expressed as a percentage of predicted value) and absolute desaturation on hypoxic challenge for all patients not on LTOT.

Predictability of desaturation in individuals from spirometry or sea level saturation

Table 3 shows examples of how individual patients with the same diagnosis, spirometry and sea level saturation can have markedly different responses to hypoxic challenge. Even in the limited numbers studied, it is clear that desaturation during HC in individuals cannot be predicted reliably from either FEV_1 or sea level SpO_2. The patient with the lowest FEV_1 in the study showed no clinically significant desaturation on hypoxic challenge.

Discussion

This paper reports our experience of assessing 131 patients (including 13 on LTOT) for their fitness to fly using hypoxic challenge and a locally derived interpretation algorithm. Patients with a range of chronic respiratory diseases, with a range of severities have been assessed.

Table 2 Results of hypoxic challenge for patients not on LTOT, broken down by diagnostic category

Primary diagnosis	Number of patients assessed	Fit to fly	Fit to fly with supplemental oxygen	Unfit to fly
COPD	74	73	26	1
Interstitial lung disease	18	71	29	0
CF or bronchiectasis	8	88	12	0
Asthma	5	100	0	0
Obstructive sleep apnoea	3	100	0	0
Previous pneumonia	3	100	0	0
Neuromuscular disease	2	50	50	0
Pulmonary vascular disease	2	50	50	0
Thoracic neoplasm	2	100	0	0
Previous ARDS	1	100	0	0

Table 3 Predictability of desaturation in individual patients from spirometry or sea level saturation

	Gender	Age	% Predicted FEV_1	Sea level SpO_2	Lowest SpO_2
Matching FEV_1	M	65	27	92	82
	M	70	26	97	94
Matching sea level SpO_2	M	73	58	94	85
	F	64	31	94	91
Lowest FEV_1 in study group	M	54	13	98	93

The first two rows of the table show pairs of patients with COPD, matched either for FEV_1% predicted or sea level SpO_2. Desaturation during hypoxic challenge is unpredictable in individuals. Even combining these predictors is unreliable; in the two patients with matching sea level SpO_2 it was the patient with the higher FEV_1 who desaturated significantly. The final row shows hypoxic challenge results for a patient with COPD who has the lowest % predicted FEV_1 in the study but yet did not desaturate below 93%.

The present data have been used to try to determine the minimum value for initial SpO_2 at which SpO_2 can be maintained at or above 90% during hypoxic challenge equivalent to cabin conditions. The results suggest (in support of the BTS guidelines) that patients with a starting SpO_2 breathing air of over 95% should be able to maintain O_2 saturation at or above 90% during air travel. For the group of patients not on LTOT with a sea level SpO_2 between 92% and 95%, however, we found that 42% of patients (25 out of 59) did desaturate below 90% on hypoxic challenge, and that 28% (7 out of 25) of those patients showing significant desaturation did not have any of the additional risk factors as suggested by the BTS. This suggests that hypoxic challenge may be of value to all patients in this group, not just those with the predefined risk factors suggested by the BTS.

For the population not requiring LTOT referred to in the present study, these results indicate that 28 patients (23% of those referred for evaluation) were at risk of desaturation below 90% during air travel. In 97% of these cases the desaturation could be prevented by supplemental O_2 at a flow of 2 L/min. Only 1 patient out of the study population of 118 not on LTOT (0.8%) was considered to be too hypoxic to fly, i.e. their SpO_2 remained $<90\%$, despite supplemental oxygen at 4 L/min.

Is hypoxic challenge necessary, or can hypoxia be predicted from other tests? Table 3 illustrates pairs of patients with COPD who have identical impairment of FEV_1 or identical sea level O_2 saturation but who respond very differently to hypoxic challenge.

A number of authors have used measurements of ground level PaO_2 in an attempt to predict in-flight PaO_2 and thus identify patients at risk of significant hypoxia. Gong et al.[1] found a good agreement between the two variables in patients with COPD and published a prediction equation allowing an estimate of in-flight PaO_2 to be made from ground level values. Dillard et al.[3] found that the addition of ground level FEV_1 improved the ability to predict accurately in-flight PaO_2 in COPD patients. Christensen et al.[10] found that sea level pO_2 is an unreliable predictor of individual response to hypoxic challenge in patients with COPD. Seccombe et al.[11] also found that resting, sea level arterial blood gas analysis was not a good predictor of the response to simulated cabin altitude in patients with either COPD or interstitial lung disease. While some of these papers report statistically significant correlations in small groups of patients between sea level measurements and measurements during hypoxic challenge, what matters to patients is their individual result. In all the published papers, and in the present much larger data set (Fig. 2 and Table 3), the scatter of individual results within the group precludes reliable prediction in individuals even when group correlations are significant. This limits the utility of predicted equations such as those described by Gong et al. and Dillard et al. when advising individual patients.

The present study could be criticised for including patients with a wide variety of respiratory conditions of varying severity; however, this reflects the actual demand for information received by a teaching hospital laboratory. Table 2 indicates that no particular diagnostic group appeared to be more at risk of hypoxia than others, within the constraints of the numbers studied.

Does desaturation worsen with prolonged flight? Most hypoxic challenge protocols are of 20–30 min duration. It is assumed that this is long enough for any physiological changes to have taken place. Akerø et al.[12] have investigated hypoxia in a group of patients with COPD during a 6 h flight and found that there was an initial fall in PaO_2 once the flight had reached cruising altitude which was maintained throughout the flight. Fischer et al.[13] have studied hypoxia in patients with cystic fibrosis at low altitude (530 m) and after 7 h at high altitude (2650 m). Patients were hypoxic at altitude but there was no trend to worsening with time and few reported any additional symptoms. Once again there were no robust individual predictors of hypoxia.

Importantly, does it matter if patients desaturate during flight? In designing the local protocol, which pre-dates the publication of the BTS guidelines, a clinical decision was made that desaturation at rest below 90% was significant hypoxia. The likelihood of additional hypoxia if these resting patients moved during flight led to a precautionary approach to patients referred with a resting SpO_2 below 90%. The link between hypoxia and actual clinical risk remains poorly understood; however, recent work has highlighted mechanisms whereby hypoxia predisposes to a variety of clinical risks. Hypoxia of the magnitude encountered in flight appears to be thrombogenic in those with other risk factors,[14] but not in healthy young subjects with no additional risk factors.[15] Pulmonary hypertension is a well-recognised consequence of hypoxia, and some of the cellular mechanisms are now being elucidated.[16] Chronic hypoxia (even mild levels) has detectable cognitive effects on children[17] and acute hypoxia at altitude affects the mental functioning of an adult aircrew,[18] even at altitudes below 10,000 feet.[19] Thus it is not unreasonable to use hypoxia as a surrogate for clinical risk even though the individual risk of adverse effects from hypoxia remains uncertain. Flight diversions for respiratory symptoms are uncommon;[20,21] however, it seems likely that those with marked desaturation (despite supplemental oxygen) will include those at most clinical risk.

In conclusion, the majority of patients referred to a routine laboratory for assessment of their fitness to fly do not develop significant hypoxia during exposure to a low oxygen environment simulating flight. Approximately one quarter of these patients will require supplemental oxygen to prevent desaturation below 90%, but the individual's need for supplemental oxygen cannot be predicted from either spirometry or sea level oxygen saturation, with the exception that hypoxic challenge appears unnecessary in patients with a sea level SpO_2 of over 95%.

Conflict of interest statement

There are no conflicts of interest.

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